Atypical Cells in Lymphomatoid Papulosis Express the Hodgkin Cell-Associated Antigen Ki-1*

Peter Kaudewitz, M.D., Harald Stein, M.D., Günter Burg, M.D., David Y. Mason, M.D., and Otto Braun-Falco, M.D.

Dermatologische Klinik und Poliklinik der Ludwig-Maximilians-Universität München (PK, GB, OB-F), Munich, F.R.G.; Institut für Pathologie, Universitätsklinikum Steglitz Freie Universität (HS), Berlin, F.R.G.; and Nuffield Department of Pathology, John Radcliffe Hospital, University of Oxford (DM), Oxford, U.K.

Lymphomatoid papulosis (LyP) is characterized by the presence of large multinucleated cells resembling Reed-Sternberg (RS) cells. Evidence of antigenic similarity between these two cell types has been sought by immunohistologic labeling of 10 biopsies from cases of LyP with monoclonal antibodies against Ki-1 and other RS and Hodgkin (H) cell-associated antigens. In all cases studied, a proportion of the large atypical cells expressed the Ki-1 antigen. On the contrary, in 20 biopsies of benign skin lesions or cutaneous T-cell lymphomas, Ki-1-positive cells were absent or only occasionally present. Furthermore the large atypical cells of LyP also expressed antigens (e.g., T3, T4, HLA-DR, IL-2 receptors) which we have previously demonstrated on RS cells in the majority of cases of Hodgkin's disease (HD). These findings, in conjunction with the observation that Ki-1 antigen expression can be induced on peripheral blood lymphocytes following exposure to phytohemagglutinin or HTLV I, provide evidence that the Ki-1 positive cells in LyP represent activated T cells as RS cells do in many cases of HD. *J Invest Dermatol 86:350–354, 1986*

The term *lymphomatoid papulosis* (LyP) was first introduced by Macaulay in 1968 [1]. Since that time numerous case reports and reviews have been published which define this clinicopathologic entity in greater detail [2]. The characteristic cutaneous lesions seen in this condition consist of transient papulonodular eruptions which show, on histologic examination, an inflammatory infiltrate in the superficial and deep dermis containing variable numbers of large atypical cells. The morphologic characteristics of these cells vary widely from case to case, and a number of predominant cytologic types have been described, including large multinucleated cells with morphologic similarities to Reed-Sternberg (RS) cells and cells containing cerebriform nuclei resembling Sézary cells [3,4].

The wide spectrum of morphologic appearances exhibited by these atypical cells has made it impossible to classify them with certainty. Immunohistologic and histochemical studies aimed at elucidating their nature have produced conflicting results, and the disease has been variously classified as a histiocytic neoplasm (based on the presence of cytoplasmic hydrolytic enzymes [5], as a cutaneous T-cell lymphoma [6,7], as a T-cell pseudolymphoma [8,9], and as a variant of Hodgkin's disease [10].

The reactivity of the atypical cells in LyP with anti-T-cell antibodies, and their ultrastructural similarities to mitogen-transformed lymphoid cells, has led to the hypothesis that they may represent stimulated T lymphocytes [11]. Evidence for this suggestion is provided by recent studies in which some of the cells have been shown to react with antibody anti-Leu-3a (anti-helper/inducer T cells) and with anti-HLA-DR [10]. However this antigen pattern may also be seen on macrophages. In this context it is of interest that recent studies have provided evidence suggesting that Hodgkin (H) and RS cells in many cases of non-lymphocyte predominance type of Hodgkin's disease (HD) are closely related to highly activated T lymphocytes [12].

In the present study we describe an immunohistologic analysis of 10 cases of LyP, aimed at assessing the possible relationship between the atypical cells seen in this condition, activated T cells, and RS cells. For this purpose a recently produced monoclonal antibody (Ki-1) reactive with RS and H cells and activated lymphoid cells, but not with macrophages has been used [13,14], in conjunction with monoclonal antibodies (anti-Tac andTü69) reactive with the interleukin 2 receptor that is expressed on activated cells [15]. In all cases studied Ki-1-positive cells were present and these cells were also positive with antibodies reactive with the interleukin 2 receptor and in most cases with anti-Leu-3a (anti-helper T cells). The Ki-1 positive cells were negative with a monoclonal antibody (25F9) directed against a macrophage-associated antigen which is not present on resting and/or activated T cells [16]. This suggests that Ki-1-positive cells are a characteristic constituent of the cellular infiltrate in LyP, and that they represent activated T cells, like RS and H cells seen in many cases of HD of nonlymphocyte predominant types [17].

MATERIALS AND METHODS

Patients Biopsies from 10 patients with LyP, and biopsies from 20 patients suffering from other types of cutaneous lesions, were obtained from the Department of Dermatology, Ludwig-Maximilians-University, Munich. The clinical diagnosis was based on the presence of papular or nodular, reddish or brownish skin eruptions, and spontaneous regression of the lesions (sometimes forming scars). The duration of the disease was between 5 months and 6 years. Histologically all cases showed a dermal infiltrate containing variable numbers of large atypical cells. Some details of the histopathologic appearance observed in individual lesions are given in Table I.

Manuscript received December 18, 1984; accepted for publication August 28, 1985.

*This work was presented in part at the 14th Meeting of the European Society for Dermatological Research, Amsterdam, The Netherlands, May 1984.

Reprint requests to Peter Kaudewitz, M.D., Dermatologische Klinik, Frauenlobstrasse 9-11, 8000 Munich 2, F.R.G.

Abbreviations:
APAAP: alkaline phosphatase anti-alkaline phosphatase
H: Hodgkin (cell)
HD: Hodgkin's disease
LyP: lymphomatoid papulosis
RS: Reed-Sternberg (cell)

0022-202X/86/$03.50

Table I. Some Histologic Features of Lymphomatoid Papulosis Lesions Studied

	Patient No.									
	1	2	3	4	5	6	7	8	9	10
Atypical cells	+ +	+ +	+ +	+ + +	+ + +	+	+	+	+	+
Mitoses	−	+	+	+	+	−	−	−	+	−
Distribution of the infiltrate										
Upper corium	+ +	+ + +	+ + +	+ +	+ +	+ +	+ +	+ + +	+ + +	+ +
Middle corium	+	+ +	+ +	+	+ +	+ +	+	+	+	+
Deep corium	−	+	+	−	−	−	−	−	+	+

Table II. Monoclonal Antibodies Used in the Present Study

Antibody	Specificity	Reference
Ki-1	Reed-Sternberg cells and activated lymphoid cells	[13]
Tü69	Interleukin 2 receptor[a]	
Anti-Tac	Interleukin 2 receptor	[15]
Tü35	HLA-DR plus DC	[18]
UCHT 1	T-cell receptor-associated molecule	[19]
Leu-3a	Inducer/helper T cells, macrophages	[20]
OKT11	E-rosette receptor	[21]
Tü102	Cytotoxic/suppressor T cells[a]	
To15	B cells	[22]
Ki-67	Proliferation-associated nuclear antigen	[23]
3C4	X-Hapten present on granulocytic cells and Reed-Sternberg cells	[24]
Na1/34	Langerhans cells, interdigitating cells, and cortical thymocytes	[25]
R4/23	Follicular dendritic cells	[26]
25F9	Macrophage-associated activation antigen	[17]

[a]Unpublished data (Dr. A. Ziegler).

Monoclonal Antibodies The antibodies used in this study are detailed in Table II. Alkaline phosphatase anti-alkaline phosphatase (APAAP) complexes were prepared as described previously [27] or obtained from DAKO PATTS Copenhagen.

Immunohistologic Labeling Immunolabeling was performed using the APAAP method as described by Cordell et al [27].

RESULTS

In all LyP lesions examined cells reactive with antibody Ki-1 were present. However the number and distribution of these cells varied widely: in 5 patients only a few Ki-1-positive cells were seen scattered among the infiltrating cells; in the remaining 5 patients Ki-1-positive cells were numerous, and formed clusters in which there were only a few Ki-1-negative cells (see Table III and Fig 1). In lesions showing the latter type of distribution, Ki-1-positive cells were larger than the other infiltrating cells (Fig 2) and they corresponded clearly in their location to large atypical cells identified in adjacent sections stained with hematoxylin and eosin.

The reactivity with other antibodies of the large atypical Ki-1-positive cells present in such atypical cell clusters was evaluated on adjacent sections. The results (detailed in Table III) show that these cells reacted with antibody Tü69 and anti-Tac (directed against the interleukin 2 receptor) and antibody Tü35 (anti-HLA-DR), although it was clear that these 2 antibodies also reacted with infiltrating cells other than those that expressed Ki-1. The large atypical cells also expressed the T-cell antigen T3 (Fig 3) in 3 of 5 cases and were even more frequently labeled by anti-helper/inducer T-cell antibody (anti-Leu-3a). The labeling reaction with these antibodies was of variable intensity. Strong reactivity was seen with antibody Ki-67 detecting proliferating cells (Fig 4). The large atypical cells in one biopsy also reacted with antibody 3C4, which labels the majority of RS cells in cases of HD. In all cases studied the large atypical cells were negative with monoclonal antibodies against B cells (To15), T suppressor cells (Tü102), interdigitating/Langerhans cells (NA1/34), dendritic reticulum cells (R4/23), and with antisera against lysozyme and the macrophage-associated antigen 25F9.

Immunohistologic labeling of the Ki-1-negative infiltrating cells

Table III. Immunophenotype of the Large Atypical Cells Seen in Lymphomatoid Papulosis Lesions

	Patient No.									
Antigen/Antibody	1	2	3	4	5	6[a]	7[a]	8[a]	9[a]	10[a]
Reed-Sternberg cell-associated antigen/Ki-1	+ + +	+ + + +	+ + +	+ +	+ +	+	+	+	+	+ +
Interleukin 2 receptor anti-Tac/Tü69	+ + +	+ + +	+ + +	+ +	+ +	−	−	−	−	−
Pan T (T3)/UCHT 1	+	+	+	−	−					
T helper cells/Leu-3a	+ +	+ + +	+	+	+					
T suppressor cells/Tü102	−	−	−	−	−					
Pan B/To15	−	−	−	−	−					
Langerhans cells/Na1/34	−	−	−	−	−					
Granulocyte-associated antigen (X-hapten)/3C4	−	+ +	−	−	−					
Macrophages/25F9	−	−	−	−	−					

[a]Lesions without clusters of atypical cells.

Key: − = No cells stained
+ = Occasional cells stained
+ + = Moderate number of cells stained
+ + + = Many cells stained
+ + + + = Great majority of cells stained

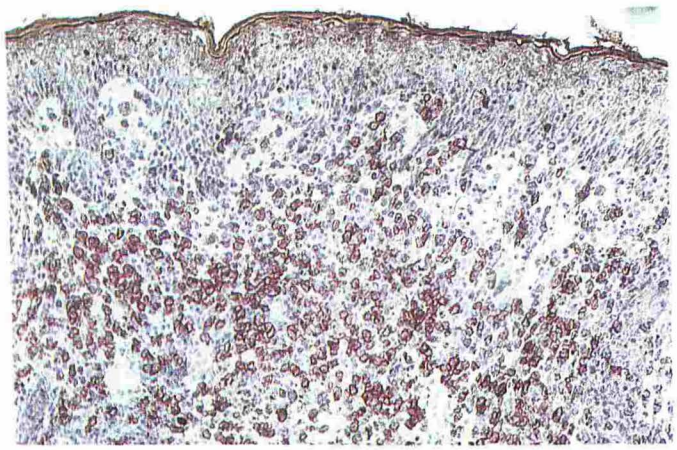

Figure 1. LyP, cyrostat section stained with monoclonal antibody Ki-1. Positive cells are numerous and form clusters. × 100.

in LyP lesions showed that most of the lymphoid cells were T lymphocytes of helper/inducer type (giving positive reactions with antibodies UCHT 1, and anti-Leu-3a) accompanied by occasional cytotoxic/suppressor T cells. Labeling with the monoclonal antimacrophage antibody 25F9 revealed the presence of numerous macrophages within the infiltrates.

Immunohistologic analysis of 20 skin biopsies from conditions other than LyP revealed no Ki-1-positive cells, with the exception of 1 lichen planus biopsy and 3 cases of mycosis fungoides, in which the Ki-1 antibody stained occasional large cells (Table IV).

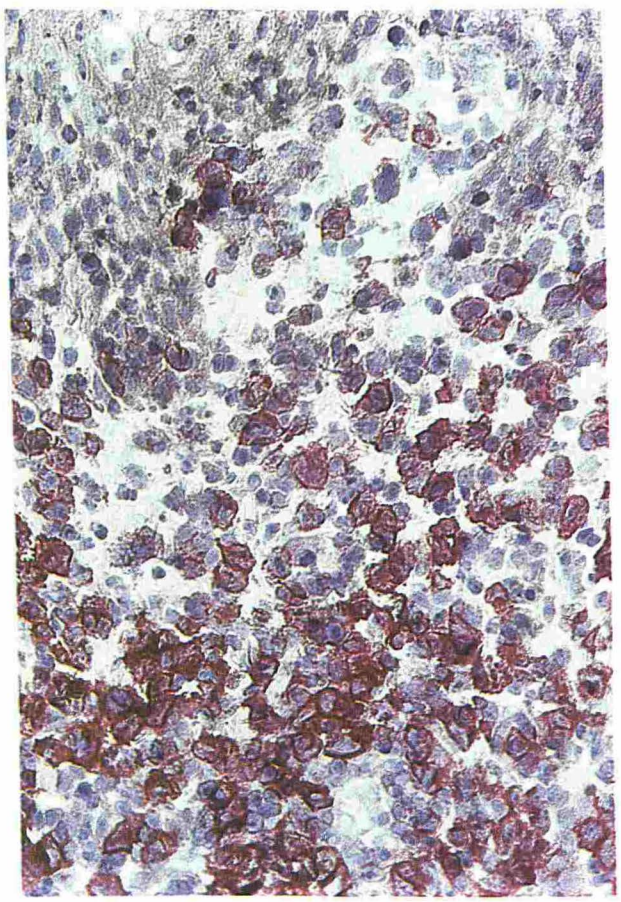

Figure 2. Detail from Fig 1. The majority of Ki-1-positive cells are larger than the other infiltrating cells. × 250.

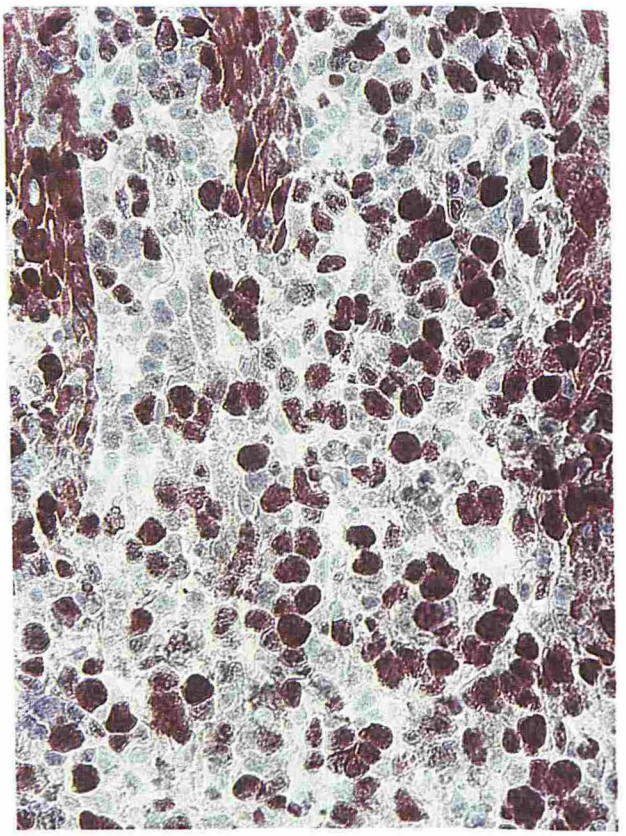

Figure 3. LyP cryostat section stained with monoclonal antibody UCHT 1. The majority of the infiltrating cells bear the T3 antigen. × 250.

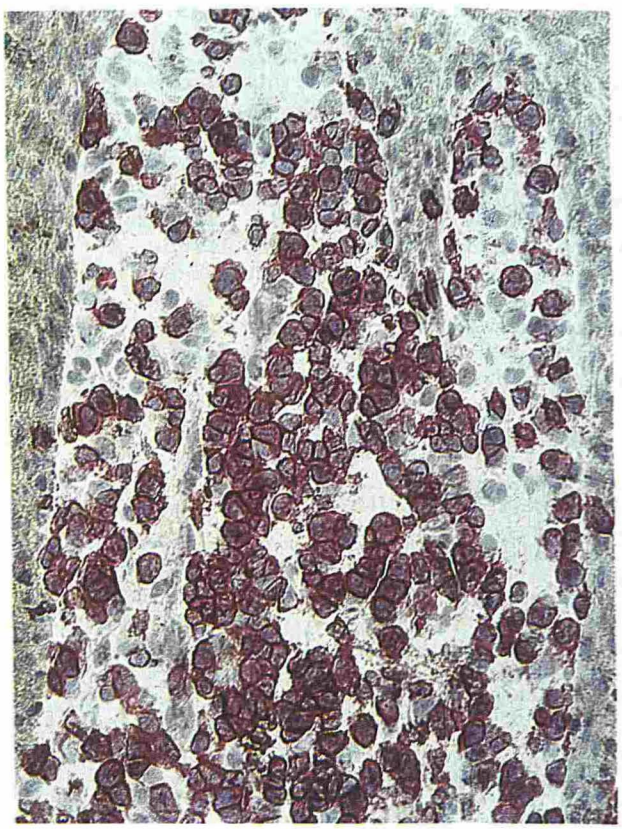

Figure 4. LyP cryostat sections stained with monoclonal antibody Ki-67. Numerous proliferating cells are present. × 250.

Table IV. Antibody Reactivity of Infiltrate Cells Present in Various Skin Lesions Other Than Lymphomatoid Papulosis

Diagnosis	No. of Cases	Ki-1	Anti-Tac	Tü69	OKT11	Tü102	TO15	Na1/34	3C4
Mycosis fungoides	1	+	ND	++	+++	+	+	++	−
	2	−	++	++	+++	ND	−	−	−
	3	−	ND	+	+++	++	−	+	−
	4	−	+++	++	+++	+	−	+	−
	5	−	ND	+	+++	+	−	+	−
	6	+		+					
	7	−	+	+	++	ND	−	+	ND
	8	+	ND	+	+++	++	−	+	−
	9	−	ND	+	+++	ND	−	+	−
Sézary's syndrome	1	++	+	+	+++	++	+	++	−
Psoriasis vulgaris	1	−	ND	+	+++	++	−	−	−
	2	−	ND	+	++	++	−	+	−
	3	−	ND	−	++	+	−	+	−
Lichen planus	1	−	ND	++	++	++	−	+	−
	2	−	ND	++	+++	++	−	+	−
Leukocytoclastic vasculitis	1	−	ND	+	++	++	−	+	−
Eczema	1	−	ND	++	+++	++	−	−	

Key: − = No cells stained
+ = Occasional cells stained
++ = Moderate number of cells stained
+++ = Many cells stained
++++ = Great majority of cells stained

DISCUSSION

Large atypical cells expressing the RS cell-associated Ki-1 antigen could be detected in all skin biopsies from cases of LyP tested. The fact that there was a wide variation in the distribution and number of cells expressing this antigen is probably accounted for by the fact that LyP lesions typically show a large variation in the number of atypical cells [3,4]. Since lesions were biopsied at random during the course of individual patient's disease, they were not at the same stage of development. It has been shown previously in histologic studies that the age of a lesion is of crucial importance in determining the number and distribution of atypical cells [28].

In all other conditions (both malignant and nonmalignant) associated with the presence of an inflammatory dermal infiltrate, Ki-1-positive cells were either absent or present only in small numbers. These findings are in accordance with previous investigations demonstrating a restricted tissue distribution of Ki-1 antigen: Ki-1 selectively stained H and RS cells in tissues affected by HD, tumor cells in a distinct type of large cell non-Hodgkin lymphoma which also expressed T- or less commonly B-cell-associated antigens, and a small proportion of large cells preferentially localized around B-cell follicles in normal lymphoid tissue [12,14]. To date no other normal tissues have been reported to contain Ki-1-positive cells. In dermal inflammatory conditions the presence of such cells seems to be confined to LyP and may therefore be a characteristic feature of this condition.

Thus Ki-1-positive cells seem to represent a common denominator of LyP and HD. Additional evidence for a relationship between LyP and HD comes from the reactivity with a number of other monoclonal antibodies (e.g., anti-Leu-3a, anti-Tac, Tü69, and anti-HLA-DR) staining both RS cells and large atypical cells in LyP.

The presence of the Ki-1 antigen and other determinants on both RS cells and large atypical cells in LyP indicating an antigenic similarity between these cell types is of obvious interest and raises the question of the cellular origin of Ki-1-positive cells in HD and LyP. Recent investigations from the authors' laboratories have demonstrated that a proportion of peripheral blood lymphocytes expresses the Ki-1 antigen after exposure to phytohemagglutinin or HTLV I. Antigenic density tended to be considerably higher on the larger and binucleated blast cells in these preparations. Macrophages of all types were consistently unreactive with the Ki-1 antibody. A varying proportion of HTLV I-transformed T lymphocytes also expressed the 3C4 antigen [12]. These observations, together with the finding that RS cells in nonlymphocyte predominance type of HD often express T-cell antigens, the 3C4 antigen, and IL-2 receptors suggests that these cells are derived from activated T cells [12]. On the same basis the atypical cells in LyP may also be categorized as being T cells which express Ki-1 and HLA-DR as a result of activation. Since the atypical cells in LyP often lack the 3C4 antigen, it appears that Ki-1-positive cells in LyP usually have not reached the activation state which H and RS cells usually represent. However the subsequent development of HD in some LyP patients [4,10] could be taken as an indication that in these cases the atypical cells proceed in their differentiation to a degree of activation which is closely related or even identical to that of H and RS cells.

REFERENCES

1. Macaulay WL: Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign—histologically malginant. Arch Dermatol 97:23–30, 1968
2. Braun-Falco O, Nikolowski J, Burg G, Schmoeckel C: Lymphomatoide Papulose. Übersicht and eigene Beobachtungen an vier Patienten. Hautarzt 34:59–65, 1983
3. Weinmann VF, Ackerman AB: Lymphomatoid papulosis. A critical review and new findings. Am J Dermatopathol 3:129–163, 1981
4. Sanchez NP, Pittelkow MR, Muller SA, Banks RM, Winkelmann RK: The clinicopathologic spectrum of lymphomatoid papulosis: study of 31 cases. J Am Acad Dermatol 8:81–94, 1983
5. Black MM, Jones EW: "Lymphomatoid" pityriasis lichenoides: a variant with histological features simulating a lymphoma. A clinical and histopathological study of 15 cases with details of long term follow up. Br J Dermatol 86:329–347, 1972
6. Schneiderman P, Edelson R, Lutzner M, Guillino M, Green I: Lymphomatoid papulosis: immunologic and ultrastructural studies (abstr). J Invest Dermatol 64:209–210, 1975
7. Lutzner M, Edelson R, Schein P, Green I, Kirkpatrick C, Ahmed A: Cutaneous T-cell lymphomas: The Sézary syndrome, mycosis fungoides, and related disorders. Ann Intern Med 83:534–552, 1975
8. Burg G, Hoffmann-Fezer G, Nikolowski J, Schmoeckel C, Braun-Falco O: Lymphomatoid papulosis. A cutaneous T-cell pseudolymphoma. Acta Derm Venereol (Stockh) 61:491–496, 1981

9. Braun-Falco O, Burg G: Die lymphomatoide Papulose als Modell eines Psuedolymphoms. Hautarzt 34 (suppl VI):69–71, 1983

10. Willemze R, Schefer E, Ruiter DJ, van Vloten WA, Meijer CJLM: Immunological, cytochemical and ultrastructural studies in lymphomatoid papulosis. Br J Dermatol 108:381–394, 1983

11. Jimbow K, Kato M, Sugiyama S: Immunohistochemical and electron microscopic characterization of lymphomatoid papulosis. J Dermatol (Tokyo) 5:113–125, 1978

12. Stein H, Mason DJ, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, Gatter K, Falini B, Delsol G, Lemke H, Schwarting R, Lennert K: The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue—evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 66:848–858, 1985

13. Schwab U, Stein H, Gerdes J, Lemke H, Kirchner H, Schaadt M, Diehl V: Production of monoclonal antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's lymphoma and subset or normal lymphoid cells. Nature 299:65–67, 1983

14. Stein H, Gerdes J, Schwab U, Lemke H, Mason DY, Bartels H, Ziegler A: Evidence for the detection of the normal counterpart of Hodgkin and Sternberg-Reed cells. Haematol Oncol 1:21–29, 1983

15. Uchiyama T, Broder S, Waldmann TA: A monoclonal antibody (Tac) reactive with activated and functionally mature T cells. 1. Production of anti-Tac monoclonal antibody and distribution of Tac (+) cells. J Immunol 126:1393–1397, 1981

16. Zwadlo G, Bröcker EB, von Bassewitz DB, Feige U, Sorg C: A monoclonal antibody to a differentiation antigen present on mature human macrophages and absent from monocytes. J Immunol 134:1487–1492, 1985

17. Stein H, Gerdes J, Schwab U, Lemke H, Mason DY, Ziegler A, Schienle W, Diehl V: Identification of Hodgkin and Sternberg Reed cells as a unique cell type derived from a newly-detected small cell population. Int J Cancer 30:445–459, 1982

18. Ziegler A, Uchanska-Ziegler B, Zeuthen I, Wernet P: HLA antigen expression at a single cell level on a K 562 and B cell hybrid: an analysis with monoclonal antibodies using bacterial binding assays. Somatic Cell Genet 8:775–789, 1982

19. Beverley PCL, Callard RE: Distinctive functional characteristics of human T lymphocytes defined by E rosetting as a monoclonal anti-T cell antibody. Eur J Immunol 11:329–334, 1981

20. Evans RL, Lazarus H, Penta AC, Schlossman SF: Two functionally distinct subpopulations of human T cells that collaborate in the generation of cytotoxic cells responsible for cell-mediated lympholysis. J Immunol 120:1423–1428, 1978

21. Veibi W, Greaves MF, Schneider C, Koubek K, Janossy G, Stein H, Kung P, Goldstein G: Monoclonal antibodies OKTM and OKTMA have pan-T reactivity and block sheep erythrocyte "receptors." Eur J Immunol 12:81–86, 1982

22. Stein H, Gerdes J, Mason DY: The normal and malignant germinal centre. Clin Haematol 11:531–559, 1982

23. Gerdes J, Schwab U, Lemke H, Stein H: Production of a mouse monoclonal antibody reactive with human nuclear antigen associated with cell proliferation. Int J Cancer 31:13–20, 1983

24. Schienle HW, Stein H, Muller-Ruchholtz W: Neutrophil granulocytic cell antigen defined by a monoclonal antibody—its distribution within normal haemic and non haemic tissue. J Clin Pathol 35:956–966, 1982

25. McMichael AJ, Pilch JR, Galfre G, Mason DY, Fabre JW, Milstein C: A human thymocyte antigen defined by a hydbrid myeloma monoclonal antibody. Eur J Immunol 9:205–210, 1979

26. Naiem M, Gerdes J, Abdulaziz Z, Stein H, Mason DY: Production of a monoclonal antibody reactive with human dendritic reticulum cells and its use in the immunohistological analysis of lymphoid tissue. J Clin Pathol 36:167–175, 1983

27. Cordell JL, Falini B, Erber WN, Ghosh AK, Abdulaziz Z, MacDonald S, Pulford KAF, Stein H, Mason DY: Immunoenzymatic labelling of monoclonal antibodies using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (APAAP complexes). J Histochem Cytochem 32:219–229, 1984

28. Willemze R, Meyer CJLM, von Vloten WA, Schefer E: The clinical and histological spectrum of lymphomatoid papulosis. Br J Dermatol 107:131–144, 1982